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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
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Declarations under Rule 4.17:

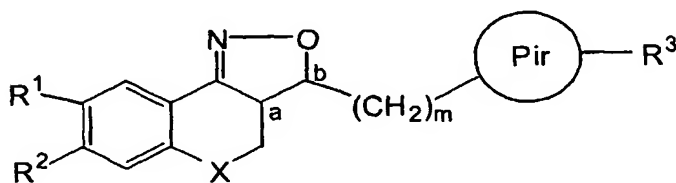
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: C-SUBSTITUTED TRICYCLIC ISOXAZOLINE DERIVATIVES AND THEIR USE AS ANTI-DEPRESSANTS



(1)

(57) Abstract: The invention concerns substituted tricyclic isoxazoline derivatives according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, more in particular tricyclic dihydrobenzopy-

ranoisoxazoline, dihydroquinolinoisoxazoline, dihydronaphthalenoisoxazoline and dihydrobenzothiopyranoisoxazoline derivatives substituted on the phenylpart of the tricyclic moiety with at least one radical that is attached to the phenyl radical by a carbon-carbon bond as well as processes for their preparation, pharmaceutical compositions comprising them and their use as a medicine, in particular for treating depression, anxiety, movement disorders, psychosis, Parkinson's disease and body weight disorders including anorexia nervosa and bulimia, wherein all variables are defined in Claim 1. (I) The compounds have surprisingly been shown to have selective serotonin (5-HT) reuptake inhibitor activity in combination with additional α_2 -adrenoceptor antagonist activity and show a strong anti-depressant and/or anxiolytic activity and/or antipsychotic and/or a body weight control activity without being sedative. Also, in view of their selective serotonin (5-HT) reuptake inhibitor as well as α_2 -adrenoceptor antagonist activity, compounds according to the invention are also suitable for treatment and/or prophylaxis in diseases where either one of the activities alone or the combination of said activities may be of therapeutic use.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50374

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/04 A61K31/424 A61P25/24 A61P25/16 A61P25/18
/(C07D498/04, 311:00, 261:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 02 066484 A (LANGLOIS XAVIER JEAN MICHEL ; BAKKER MARGARETHA HENRICA MARI (BE);) 29 August 2002 (2002-08-29) claims 1,2; examples 216,349; tables	1-16
P, Y	ANDRES, J. IGNACIO ET AL: "Synthesis of 3a,4-dihydro-3H-1!benzopyrano'4,3-c!isoxa zoles, displaying combined 5-HT uptake inhibiting and .alpha.2-adrenoceptor antagonistic activities: a novel series of potential antidepressants" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2003), 13(16), 2719-2725 , XP002261582 examples 4-7; table 1	1-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

14 November 2003

Date of mailing of the international search report

28/11/2003

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INTERNATIONAL SEARCH REPORT

International Publication No
PCT/EP 97/50374

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 082878 A (JANSSEN PHARMACEUTICA NV ;BAKKER MARGARETHA HENRICA MARI (DE); ALC) 9 October 2003 (2003-10-09) claim 1; examples ---	1-16
A	WO 97 25317 A (HOECHST MARION ROUSSEL INC) 17 July 1997 (1997-07-17) claim 1; examples 3,5,6,10 ---	1-16
A	WO 95 07893 A (MERCK SHARP & DOHME ;DAVEY WILLIAM BARNABY (GB); LEESON PAUL DAVID) 23 March 1995 (1995-03-23) claim 5; example 4 ---	1-16
A	EP 0 885 883 A (YOSHITOMI PHARMACEUTICAL) 23 December 1998 (1998-12-23) page 24 -page 26; examples 48-62,82,107 ---	1-16
A	EICHINGER K ET AL: "A CONVENIENT SYNTHESIS OF 3- AND 3,4-SUBSTITUTED 4,5-DIHYDROISOXAZOLE-5-ACETIC ACIDS" SYNTHETIC COMMUNICATIONS, MARCEL DEKKER, INC., BASEL, CH, vol. 27, no. 16, 1997, pages 2733-2742, XP001006906 ISSN: 0039-7911 example 4B -----	1-6

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/50374

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound.
2. ☒ Claims Nos.: 6
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 6

Present claim 6 relate to a product defined by reference to a desirable characteristic or property, namely the ability to be degraded in vivo to yield a compound having the general formula (I). The claim covers all products having this characteristic or property, but does neither give a technical teaching as to the possible structures involved nor means for verifying whether a compound has this property. The claim therefore lacks clarity (Article 6 PCT) to such an extent that a search for possible and hypothetical structures was impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP/50374

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